

RNA Families

The RNase P family

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Ribonuclease P (RNase P) is a ribonucleoprotein comprised of a catalytic RNA subunit and one or several protein subunits. RNase P is best known for its role in 5'-processing of tRNA precursors. RNase P enzymes from almost all forms of life, including protein-synthesizing organelles, contain an RNase P with a conserved, homologous RNA. Five distinct structure classes of RNase P RNAs have been identified in bacteria and archaea; eukaryotic RNase P RNAs are not yet sufficiently well surveyed for structure classes to be defined. Here we will examine the structure variations in RNase P RNAs in bacteria, archaea, eukaryotes, plastids and mitochondria with special emphasis on the functional roles these unique secondary structures perform.

Introduction

Ribonuclease P (RNase P) is an ancient ribonuclease, arising before the last common ancestor and thought to be a relic of the RNA world. The RNase P holoenzyme is a ribonucleoprotein complex comprised of an RNA subunit and one or more protein subunits. The RNA, not the associated protein(s), is the catalytic subunit; RNase P is a truly catalytic RNA. RNase P enzymes from all three domains of life (bacteria, archaea and eukarya) have a homologous RNA subunit, and with a single known exception (that of the human mitochondrion, see below) this RNA is found in all organisms and is an essential component of life.

RNase P is best known for its role in the maturation of tRNA. RNase P recognizes the mature region of the precursor-tRNA (pre-tRNA) substrate and cleaves it at the location of the 5' end, generating the 5'-mature tRNA and a leader fragment. RNase P is also responsible for the 5' maturation of other RNAs, e.g., 2S, 4.5S, tmRNAs and snoRNAs.¹⁻⁶ It has also been shown to cleave riboswitches in *E. coli* and *Bacillus subtilis*.⁷⁻⁹

Five distinct structural classes of RNase P RNAs (types A, type B, type C, type M and type T) have been defined, and many less well-defined types and subtypes have been observed in nature. Here we will examine the structure variations in RNase P RNAs

in bacteria, archaea, eukaryotes, plastids and mitochondria with special emphasis on the functional roles these unique secondary structures perform.

Bacterial RNase P RNA

In bacteria, the RNase P holoenzyme is composed of a single RNA (ca. 400 nts) and a single small protein subunit (ca. 14 kDa). The secondary structure of RNase P RNA in bacteria has been well-established primarily on the basis of comparative analysis of several hundred sequences.¹⁰⁻¹³ Two distinct secondary structure types predominate in bacteria: Type A and Type B. Within each type, the RNAs share a common conserved "body plan", often decorated by volatile insertions and deletions. Each of the types can be further separated into subtypes that vary in conserved specific elements.

All bacterial RNase P RNAs are homologous, and share an expanded version of the universal "minimum consensus" or "core" secondary structure (Fig. 1).^{14,15} That this core contains all of the elements required by the enzyme for substrate recognition and catalysis has been shown by the demonstration that this RNA efficiently processes pre-tRNAs under appropriate conditions.¹⁵ This core is only 225 nucleotides in length, about half the length of typical bacterial RNase P RNAs. Although the base pairs within this "core" are conserved in all cases (by definition), less than 20% of the individual nucleotides are conserved in identity in all cases. The most conserved nucleotides are concentrated in P4 and the surrounding nucleotides [Conserved regions (CR) I and V], the large loop between P11 and P12 (CR II and III), and in the region surrounding P18 (CR IV). The catalytic center of the RNA is composed of CR I, IV and V. The conserved secondary structures of the loop distal P15 (L15) and the cruciform created by P7, P8, P9 and P10. L15 is responsible for recognition of the 3' NCCA tail of the pre-tRNA substrate, at least in part directed by base pairing to a conserved GGU sequence in L15 (see Fig. 2).^{16,17} The cruciform is involved in recognition of the substrate T-loop, but the details of this interaction are not known.

Bacterial RNase P RNAs are comprised of two independently evolving domains, separated by P7. The RNA upstream and downstream of P7 contains all of the essential catalytic sequences and structures, and so is referred to as the catalytic or "C-domain". Changes in the RNA bound at each end by the two strands of P7 (the loop of P7) alter substrate specificity, and so is known as the specificity or "S-domain".

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In all bacterial RNase P enzymes examined, the RNA subunit is associated with a single, small conservative protein. This protein, encoded by the *mpaA* gene, has an unusual left-handed $\beta\alpha\beta$ crossover connection and a large central cleft.¹⁸ This secondary structure is shared by ribosomal protein S5 and ribosomal translocase elongation factor (EF-G), suggesting that these proteins evolved from a common ancestry component of the ancient translational machinery.¹⁸

Bacterial type A RNase P RNAs. Type A (Ancestral) RNase P RNAs are present throughout both bacterial and archaeal diversity, and so presumably was present in the common ancestor of these organisms. Other types of bacterial (or archaeal) RNase P RNAs are confined to specific single phylogenetic groups. Bacterial type A RNase P RNAs are most commonly represented by that of *Escherichia coli* (Fig. 2). Bacterial type A RNAs are distinguished from type B (the other major structure class in Bacteria) by the presence of P16, P17 and P6 (creating a second pseudoknot in the structure of the RNA, the first being P4) and the absence of P5.1, P10.1, P15.1 and P15.2.¹⁹ Most bacterial type A RNAs also contain P13, P14 and P18. P19, a phylogenetically volatile structure, is present in many RNase P RNAs of any structure class, but is not present in that of *E. coli*. The elements of structure present in bacterial type A RNAs but absent in type B, or visa versa, and most notably P13/P14 and P18, serve important roles in stabilizing the core of the RNA, but play no direct role in either substrate binding or catalysis.

Bacterial type A RNase P RNAs can be further divided into subtypes on the basis of variation in key structural elements. We propose to formalize these subtypes here.

The most common subtype of bacterial type A RNA, type "A1", is exemplified by that of *E. coli*. These RNAs are composed of at least 18 helices, P1–P18. Many type A1 RNAs contain additional idiosyncratic helices, most commonly P19 and hairpins inserted into the joining regions between P15 and P16 (J15/16) or P16 and P17 (J16/17 or J17/16). The internal loop distal to P15 (L15, or more formally J15/16 and J16/15) is symmetric or nearly symmetric, and contains a highly conserved motif RGGUA that has been shown to recognize and base pair to the NCCA tail of the pre-tRNA substrate (the base pairing nucleotides are underlined).^{16,17}

The type "A2" RNase P RNAs of most species of β -proteobacteria lack both P13 and P14.¹² Associated with this loss are changes in the conserved sequences at the base of P12 including the loss of the bulged AA doublet. The bases of P13 and P14 stack to create a single structural element; the loop of P14 interacts with P8, providing stabilization of the P7/P8/P9/P10 cruciform. However, although there are no potentially compensatory additional elements in type A2 RNAs, there is no evidence that type A1 and A2 RNAs are functionally distinct.

In Bacteria of the phylum Chlamydiae, RNase P RNA is similar to type A1 except that the critical L15 does not comply with the consensus.^{20,21} In these type "A3" RNAs, this loop is a small highly asymmetric internal loop with only a single G in J15/16 and ca. 5 nucleotides in J16/15 that lacks the consensus RGGUA substrate binding sequence.²² These RNAs are nevertheless capable

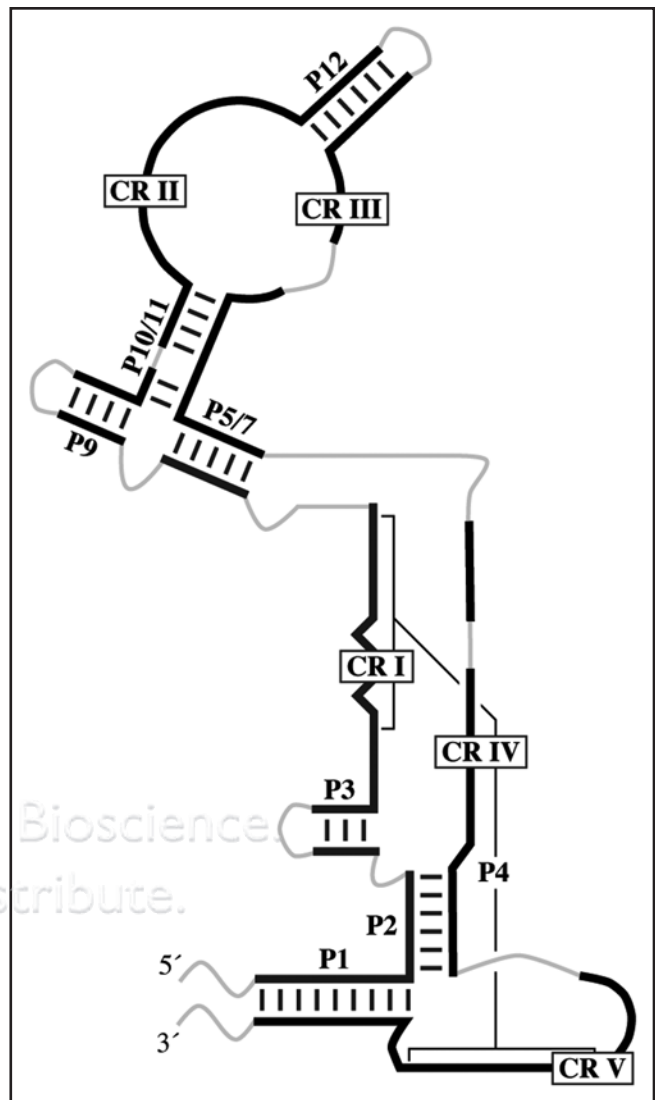


Figure 1. Consensus secondary structure of bacterial, archaeal and eukaryotic nuclear RNase P RNAs. Elements of structure absent in only single, small evolutionary groups are included: P12 (absent in *Mycoplasma fermentans*), P2 and everything distal to P10/11 (reduced or absent in *Pyrobaculum*). Grey lines indicate connections that vary in structure between conserved elements. Helices are labeled P1–12 and conserved sequence regions are labeled CR I–V.^{19,51}

of substrate recognition, but the differences in substrate binding efficiency and mechanism have not been investigated. This change in RNase P RNA may be related to the fact that tRNA genes in Chlamydiae do not routinely encode the NCCA tail.

The type "A4" RNase P RNAs of cyanobacteria are also unusual in L15, which is asymmetric and much larger than in type A1 RNAs.^{23,24} J16/15 is especially large and U-rich, and lacks the RGGUA sequence. This region often also contains idiosyncratic hairpin insertions. In addition, most cyanobacterial RNase P RNAs contain greatly enlarged P12s by the expansion of short tandemly repeated repetitive (STRR) sequences.^{23,24} Because no part of the RNA other than P12 contains STRR sequences, and because removal of these elements results in no significant change

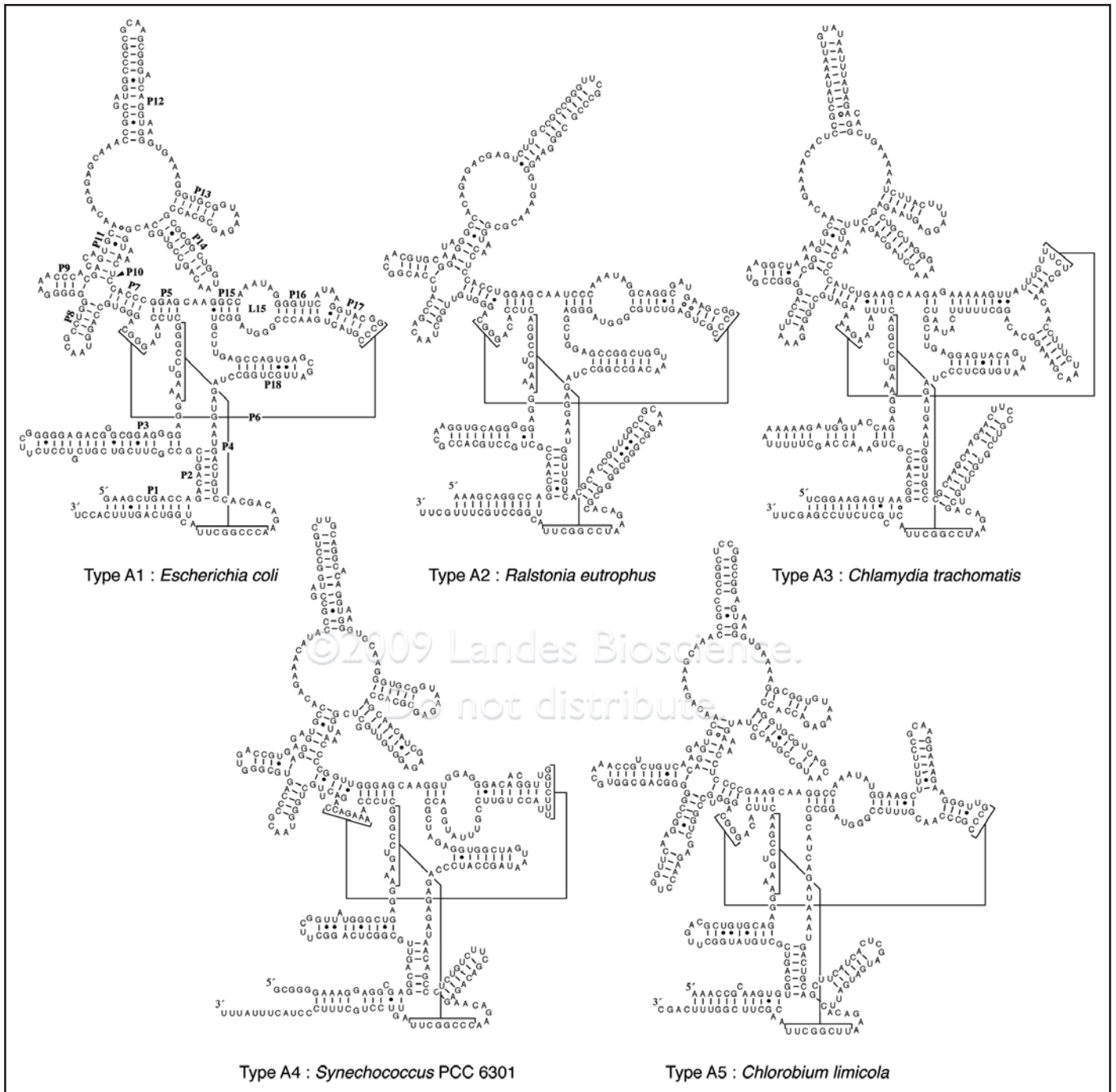


Figure 2. Representative bacterial type A RNase P RNAs. Type A1, exemplified by that of *E. coli*, is common throughout bacterial phylogeny. Type A2 (lacking P13 and P14) is found in most β -proteobacteria. Type A3 (with an altered L15 internal loop, in which the substrate 3'-NCCA tail is recognized) is found in Chlamydiae. Type A4 (also with an altered L15) is present in cyanobacteria. Type A5 (lacking P18) is present in Chlorobi and Aquificae. Structures are modified from the RNase P Database.²⁰

in catalytic activity, it seems that these extra elements are tolerated rather than inferring any evolutionary distinction.^{23,24}

The type "A5" RNase P RNAs of the bacterial phyla Chlorobi (the green sulfur bacteria) and Aquificae (except for *Aquifex aeolicus*, which may not contain a traditional RNase P) lack P18, and there is a concomitant increase in the length of P8.²⁵ P18 in other bacterial RNase P RNAs is rooted in CR IV, is conserved in

length, and its loop (L18) interacts with P8.²⁵ This interaction, like that of P14 with P8, stabilizes this critical helix.²⁵ However, also like type A2 RNase P RNAs, the loss of this stabilizing element has no significant affect on substrate affinity, although in the case of type A5 RNAs this is presumably because of compensatory increases in the length of P18 (resulting in additional stabilizing contacts elsewhere) and perhaps P9.

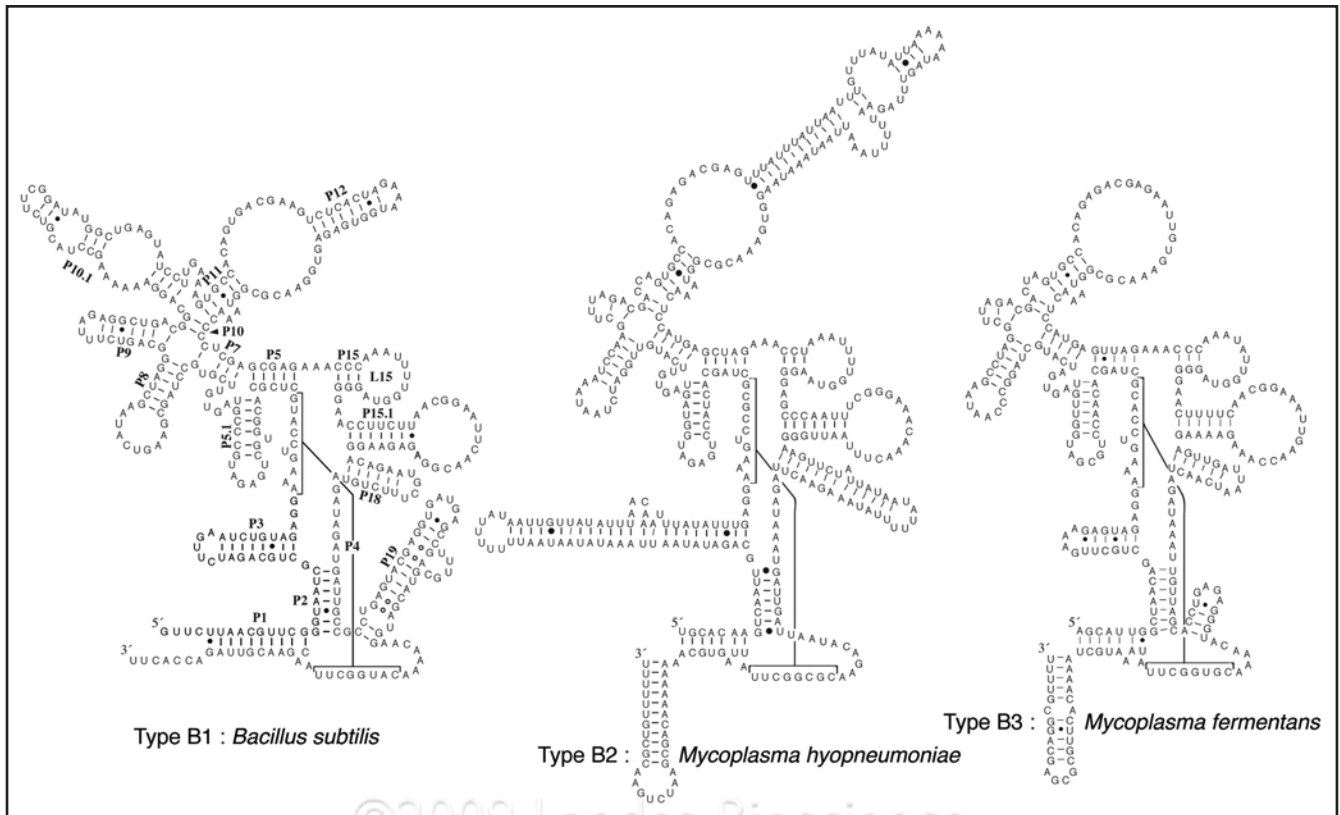


Figure 3. Representative bacterial type B RNase P RNAs. Type B1, exemplified by that of *B. subtilis*, is common amongst the Firmicutes. Type B2 (lacking P10.1) is found in some Mycoplasma species. Type B3 (lacking P12) is found only in *M. fermentans*. Structures are modified from the RNase P Database.²⁰

Type B RNase P RNAs. Most members of the bacterial phylum Firmicutes (the low G + C Gram-positive bacteria) have type B RNase P RNAs (Fig. 3). These RNAs lack the non-core secondary structural elements found in Type A RNAs: P6, P13, P14, P16, P17 and P18.²⁶ Replacing these structures are P5.1, P10.1, P15.1 and P15.2. Despite this substantial difference in secondary structure, the RNase P proteins in these organisms are indistinguishable from those of type A RNase Ps, and type A and type B RNase P RNAs have been shown to be functionally interchangeable both in vitro and in vivo.²⁷

The typical type B RNase P RNA, type “B1”, is exemplified by that of *Bacillus subtilis*. The P6/P16/P17 structure of type A RNAs is replaced by P5.1, P15.1 (and a loop-loop interaction between these) and P15.2.²⁶ Stabilization of P8, which is attributed to interactions with P14 and P18 in most type A RNAs, is accomplished by a lengthening of P8 and an additional interaction of this loop (L8) with P4. P12 in type B RNAs is conserved in length, and interacts with an internal loop in an additional type B helix, P10.1.

Within the Firmicutes, the RNase P RNAs of some members of the class Mollicutes (*Mycoplasma* and relatives; sometimes considered a separate bacterial phylum Tenericutes) are of typical type B1, but others lack P10.1 and have enlarged P12, P15.2 and P3.^{26,28} The biochemical properties of these type “B2” RNAs have not been investigated in any detail, but they are catalytically proficient.²⁹

An extreme case of modification of the type B RNA is the type “B3” RNase P RNA of *Mycoplasma fermentans*, which lacks the otherwise universally present (except in type T RNAs, see below) P12 as well as P10.1.³⁰ Unlike the type B2 RNA, P3 and P15.2 are not enlarged, and P9 is reduced to a minimum.³⁰ The *M. fermentans* RNA is the smallest known naturally-occurring bacterial RNase P RNA.

Type C RNase P RNA. The type “C” RNase P RNAs found in *Thermomicrobium roseum* resembles an intermediate between type A and B RNAs, although this organism is a member of the phylum Chloroflexi and not specifically related to the Firmicutes in which the type B RNAs reside (Fig. 4). The *T. roseum* RNase P RNA retains the ancestral P16, P17, P6 structure of type A RNAs, as opposed to the type B P5.1/P15.1 alternative, but like type B RNAs contains a P10.1-like elements, lacks P13 and P14, and contains a P15.2.¹⁹ Although this RNA resembles type B RNAs in these aspects of structure, the *sequence* of this RNA is *not* related to that of the type B RNAs, and so this probably represents an example of structural convergent evolution rather than horizontal gene transfer.¹⁹ Other Chloroflexi have type A1 RNase P RNAs, but with the addition of a P15.2-like helix.

Archaeal RNase P RNA

In archaea, the RNase P holoenzyme is composed of a single RNA molecule and several protein subunits.³¹ Most archaeal

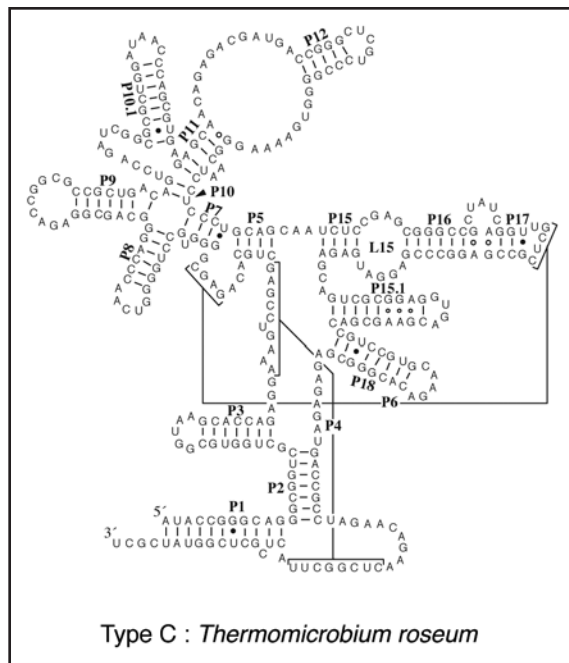


Figure 4. Bacterial type C RNase P RNA. Type C, found only in *Thermomicrobium* (a member of the Chloroflexi), retains P6, P16 and P17 from the ancestral type A, but lacks P1 and P14, and incorporates P10.1 and P15.1 from type B RNAs. Structure modified from the RNase P Database.²⁰

RNase P RNAs are similar to bacterial type A RNAs, and so this form of the RNA is presumably ancestral in the archaea. The other recognized RNase P RNA types in archaea, type M and type T, are confined to specific phylogenetic groups.

Archaeal RNase P RNAs typically have larger P12 structures than do Bacteria, including an internal loop containing conserved purine-rich sequences.

Most archaeal RNase P RNAs associate with four protein subunits that resemble in structure and sequence the four “core” eukaryotic RNase P proteins and *not* the single bacterial RNase P protein subunit.³¹ It is thought that the RNase P of the last common ancestor of all three domains of life had an RNA-only RNase P, which was independently supplemented by these proteins in the bacterial branch on one hand, and the archaeal/eukaryal branch on the other.

Archaeal type A RNase P RNA. Archaeal type A RNase P RNAs are remarkably similar to bacterial type A RNase P RNAs, but are distinguished by the lack of P18 and P13/P14 (Fig. 5).^{32,33} Of course P18 is also absent in the bacterial type A5 RNAs, and P13/P14 are absent in bacterial type A2. The L15 sequence and structure is more variable in archaea than in bacteria, but any subtypes based on this variation are not yet clear.

Despite this structural similarity between bacterial type A RNAs and those of Archaea, it was previously widely thought that the archaeal RNase P RNAs were dependent on their associated proteins for catalytic activity, as are their homologues in eukaryotes. However, most archaeal RNase P RNAs (those that most closely resemble the RNAs of Bacteria) *are* catalytically active in the absence of protein, but this activity is poor and requires

extreme ionic conditions.³⁴ As in Bacteria, the protein subunits in the archaeal enzymes seem not to contribute directly to catalysis, but contribute substantially toward stabilization of the superstructure of the RNA.

Type M RNase P RNAs. The type “M” RNase P RNAs of the archaeal phyla Methanococci and Archaeoglobi are reduced from the type A structure, lacking essential elements of the RNA: P8 (which is essential for substrate T-loop recognition) and L15 (required for substrate 3'-NCCA tail recognition) (Fig. 5).¹¹ These RNAs, therefore, have lost all elements of the RNA outside of the catalytic site that are known to be essential for specific substrate binding, and as might be predicted are devoid of catalytic activity in the absence of protein. How these holoenzymes compensate for the absence of these essential functional elements is not known. Type M RNAs also lack the P16/P17/P6 structure common to other type A RNAs both in bacteria and archaea, and have an unusually long and regular fused P10/P11.¹¹

Type T RNase P RNAs. The type “T” RNase P RNAs of some members of the archaeal Order Thermoproteaceae grossly resemble archaeal type A RNAs (with some unusual sequences), except that they have lost nearly the entire S-domain; the only structural elements distal to P7 are P9 and P10 (Fig. 5).³⁵ P8 is absent and P10 (if this helix really is homologous to P10) is capped with a small loop; the remainder of the S-domain (P11, J11/12 and J12/11 including CR II and CR III, and P12) is absent. Nevertheless this RNA *is* catalytically proficient. This reduction in the size of type T RNase P RNAs might be associated with the reduction of most pre-tRNA 5'-leaders in these organisms to only a few nucleotides.

Eukaryotic RNase P RNAs

Eukaryotes have distinct RNase P enzymes in the nucleus, mitochondria, and plastids. These RNase P enzymes are not as well understood as are those of bacteria or archaea. In cases where a nuclear, mitochondrial or plastid RNA subunit has been identified and tested, they have only trace or no activity in the absence of their associated proteins. The nuclear holoenzyme is comprised of at least 6–12 protein subunits, far more than is found in archaea (four) or bacteria (one).³¹ None of these proteins are homologous to the bacterial RNase P protein, but a core of four of these proteins *are* homologous to the conserved four RNase P proteins of the archaeal enzyme.³⁶ This implies that the protein subunits associated with the RNase P RNA evolved independently in the bacterial branch of the phylogenetic tree and in the archaeal/eukaryotic branch. Nuclear RNase P RNAs have only been surveyed systematically in fungi and chordates. Organellar RNase P RNAs in primitive microbial eukaryotes are related to their bacterial ancestors (proteobacteria and cyanobacteria), but more often are very highly altered or remain to be identified. As a result, it is perhaps premature to divide these RNAs into structure classes.

In all examined Eukaryotes, with one exception, at least two RNase P RNA types are present, one in the nucleus (nucleolus) and one in the mitochondria. In at least primitive algae, a third RNase P RNA is found in the plastid.

Nuclear RNase P RNAs share many of the RNA secondary structural elements found in other RNase P RNAs, such as: P1,

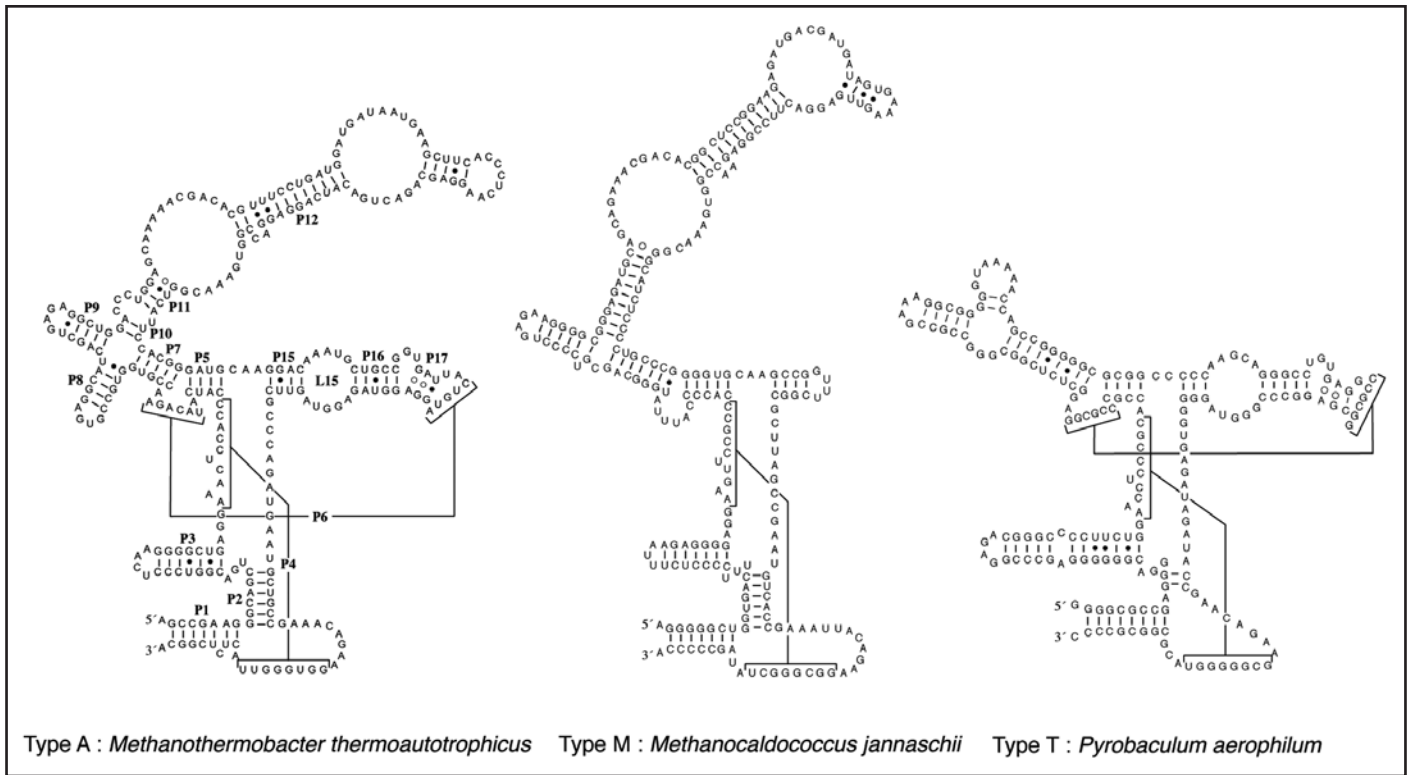


Figure 5. Representative archaeal RNase P RNAs. Archaeal type A RNA, exemplified by that of *M. thermoautotrophicus*, is similar to bacterial type A RNAs but lack P13, P14 and P18. Type M RNAs (lacking P6, P8, P16 and P17) are found in Methanococci and Archaeoglobi. Type T RNAs (lacking the S-domain) are found in the Thermoproteaceae (ref to the unpublished citation). Structures are modified from the RNase P Database.²⁰

P2, P3, P4, P7, P10/11, P12 and P15 (Fig. 6).³⁷ Some secondary structural elements are not recognizably similar in sequence or structural detail, but are found in (approximately) the same location as conserved structures in bacterial and archaeal RNase P RNAs. In order to distinguish these elements, they are labeled “eukaryal paired” regions or “eP”. Examples include eP8, eP9, eP15 and eP19. Whether these are homologous or structurally analogous to their apparent counterparts in bacteria/archaea is unclear. P3 in most nuclear RNase P RNAs contains a large internal loop near the center of the hairpin not present in bacterial and archaeal RNAs. This loop (L3) divides P3 into two distinct hairpins, P3a and P3b. This region serves as the binding site for proteins (conflicting data suggest that this is either Pop1 or a Pop6/7 heterodimer) that may recruit the other essential proteins to nucleate the assembly of the holoenzyme.^{38,39} Other RNA structures found in Archaea and Bacteria (P13, P14 and L15) are missing all together in nuclear RNase P RNAs.

Few RNase P RNAs from mitochondria have been identified and even fewer have had their secondary structure solved (Fig. 7). *Reclinomonas americana* mitochondrial RNase P RNA is primitive and recognizably similar to those of α -proteobacteria, the ancestors of mitochondria.⁴⁰ They contain all of the secondary structure elements found in α -proteobacteria except those distal of P15, including L15. The only other mitochondrial RNase P RNAs in which the secondary structures are well-resolved are the Zygomycetes. These secondary structures are highly variable in length, ranging from 188 nt to 982 nt.⁴¹ The P12 and P15 regions

of these RNAs contains remarkable variation in length, sequence and structure.⁴¹ RNase P. Ascomycete mitochondrial RNase P RNAs are, on the other hand, highly reduced in size and lack most of the sequence and structural elements conserved in other RNase P RNAs.⁴²⁻⁴⁵ The human (and presumably other metazoans) mitochondrial RNase P lacks the RNA subunit entirely; the RNase P catalytic function has been replaced by a Rube Goldberg triad of unrelated proteins.^{46,47}

The secondary structure of RNase P RNAs from primitive plastids are similar to those of cyanobacteria, from which they derive. However, homologs of RNase P RNA have not been identified in green plants or algae, and there is good evidence that these enzymes, like those of the human mitochondria, are protein-only enzymes.^{48,49}

Conclusions

RNase P RNA arose before the last common ancestor and may be a relic of the hypothetical “RNA World”. Remarkable divergence in both sequence and structure as occurred since this time, but most retain a recognizable core of sequence and structure in the RNA that constitutes the catalytic center of the enzyme. Only in two cases is a homologous RNase P RNA known to be absent: in human (and presumably other animals) mitochondria the usual RNA-containing RNase P has been replaced by an enzyme composed of three proteins that are unrelated to RNase P enzymes in other systems, but nevertheless are together responsible for the cleavage of pre-tRNA precursors and in Nanoarchaem tRNAs are

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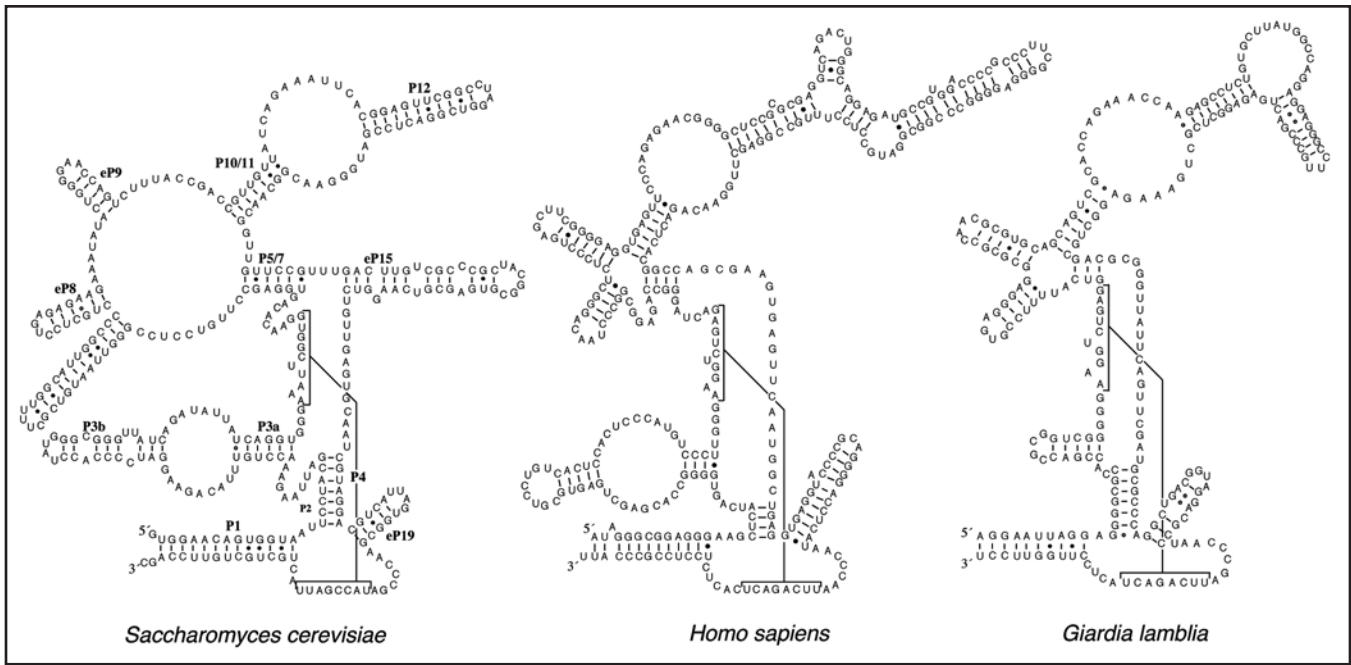


Figure 6. Representative eukaryotic nuclear RNase P RNAs. The fungal nuclear RNase P RNAs are exemplified by that of *S. cerevisiae*. The vertebrate nuclear RNase P RNAs are exemplified by that of *H. sapiens*. The nuclear RNase P RNAs of other phylogenetic groups of eukarya are not well-surveyed, but the diversity of structure is exemplified by that of the diplomonad *G. lamblia*. Structures are modified from the RNase P Database.²⁰

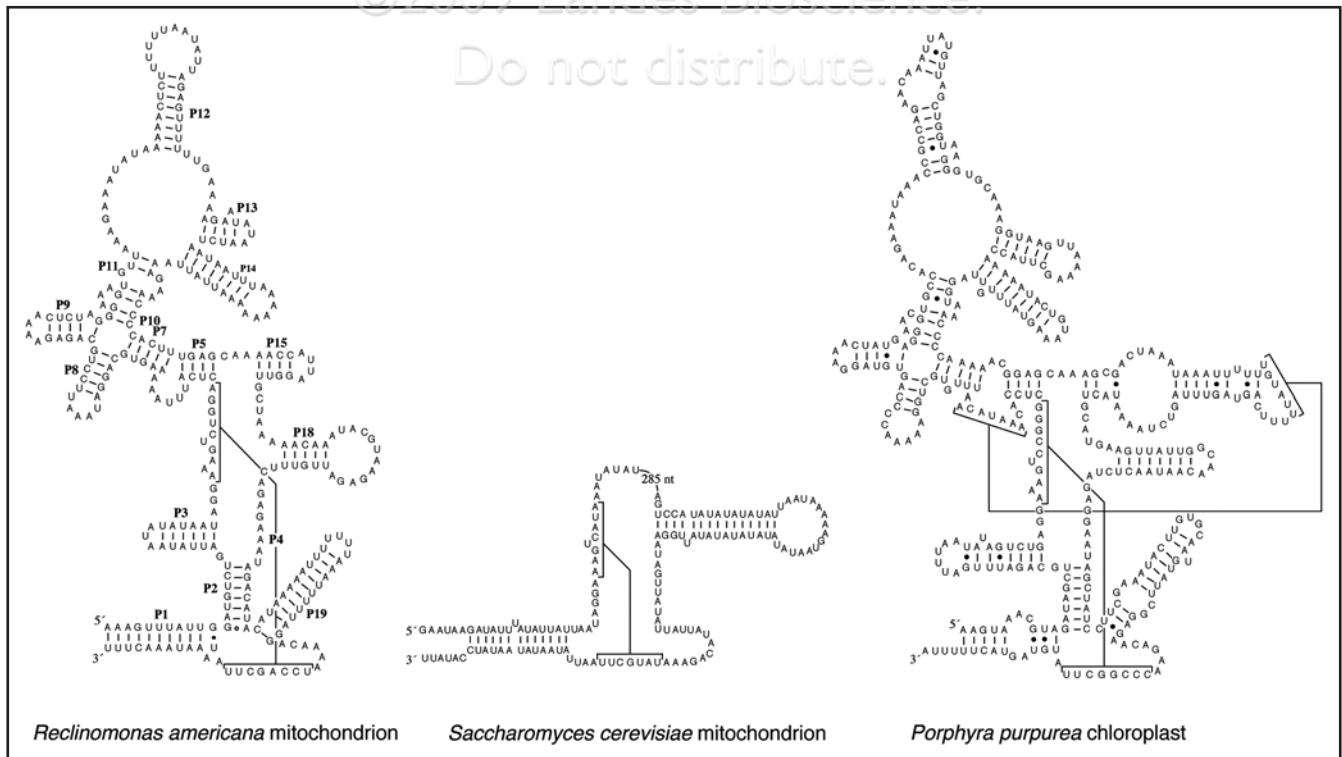


Figure 7. Representative organellar RNase P RNAs. Mitochondrial RNase P RNAs are extremely diverse, and in most cases their secondary structures are not well resolved. The RNase P RNA from the *R. americana* mitochondrion is an example of a mitochondrial RNA that has retained its similarity to those of their bacterial ancestry. The RNase P RNA from the *S. cerevisiae* mitochondrion is an example of a highly-derived (degenerate?) mitochondrial RNase P RNA. Plastid RNase P RNAs in non-green algae, exemplified here by that of *P. purpurea*, are similar to those of their cyanobacterial ancestry; no RNase P RNAs have been identified in green plants or algae, and these plastids may lack an RNA-containing RNase P (see text). Structures are modified from the RNase P Database.^{20,44}

transcribed without leaders and the RNase P RNA and associated proteins has been dispensed with entirely.^{46,50} It is also likely that the RNase P RNA has been replaced in the RNase P enzyme of the plastids of green plants, but the components of this enzyme have yet to be determined. All other organisms and protein-synthesizing organelles retain this ancient RNA enzyme.

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